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(54) Title: CYCLIC AMINO ACIDS AND DERIVATIVES THEREOF USEFUL AS PHARMACEUTICAL AGENTS

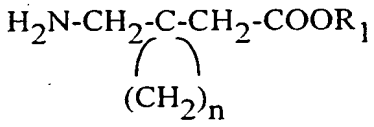
(57) Abstract

The invention is a novel series of cyclic amino acids which are useful in the treatment of epilepsy, faintness attacks, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), and inflammation, especially arthritis. A pharmaceutical composition containing a compound of the invention as well as methods of preparing the compounds and novel intermediates useful in the preparation of the final compounds are included.

CYCLIC AMINO ACIDS AND DERIVATIVES THEREOF USEFUL AS PHARMACEUTICAL AGENTS

BACKGROUND OF THE INVENTION

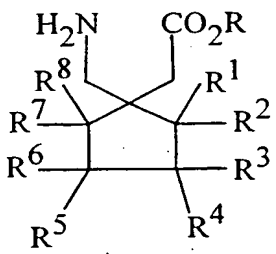
Compounds of formula



wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

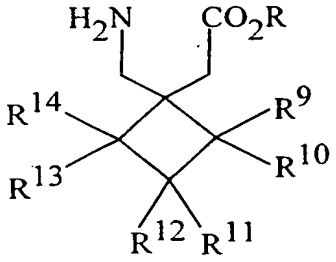
SUMMARY OF THE INVENTION

The compounds of the invention are those of formulas 1 and 1A



1

or



1A

wherein R to R^{14} are as defined below.

Preferred compounds of the invention are those of Formula I wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl straight or branched, phenyl, or benzyl.

More preferred compounds are those of Formula I wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, or benzyl.

The most preferred compounds are selected from:

(1α,3α,4α)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

trans-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-diethyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-diisopropyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-di-tert-butyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-diphenyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-dibenzyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-2,2,4,4-tetramethyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-2,2,3,3,4,4-hexamethyl-cyclobutyl)-acetic acid;
(R)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;
(S)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;
(1R-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-2,2,5,5-tetramethyl-cyclopentyl)-acetic acid;

(1α,2β,5β)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2R, 5R)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2S. 5S)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(1α,2α,5α)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

and

[1S-(1α,2β,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid.

Certain intermediates are useful in the preparation of the compounds of the invention:

(trans)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester;

(trans)-(3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid;

(±)-(trans)-7,8-Dimethyl-spiro[4.4]nonane-2-one;

present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

METHODS AND MATERIALS

Animals

Male Sprague-Dawley rats (180-250 g) were obtained from Bantin and Kingman, (Hull, U.K.). Animals were housed in groups of 6 to 10 under a 12 hour light/dark cycle (lights on at 7 hours, 0 minutes) with food and water ad libitum.

Carrageenan-induced Thermal Hyperalgesia in the Rat

Thermal hyperalgesia was assessed using the rat plantar test (Ugo Basile, Italy) following a modified method of Hargreaves, et al., 1988. Rats were habituated to the apparatus which consisted of three individual perspex boxes on an elevated glass table. A mobile radiant heat source located under the table was focused onto the desired paw and paw withdrawal latencies (PWL) recorded. PWL were taken 3 times for both hind paws of each animal, the mean of which represented baselines for right and left hind paws. At least 5 minutes were allowed between each PWL for an animal. The apparatus was calibrated to give a PWL of approximately 10 s. There was an automatic cutoff point of 20 s to prevent tissue damage. After baseline PWLs were determined, animals received an intraplantar injection of carrageenan (100 µL of 20 mg/mL) into the right hind paw. PWLs were reassessed following the same protocol as above 2-hour post-carrageenan (this time point represented the start of peak hyperalgesia) to ascertain that hyperalgesia had developed. Test compounds were administered orally (in a volume of 1 mL/kg) at 2.5 hours after carrageenan. PWLs were reassessed at various times after drug administration.

A Model of Anticonvulsant Efficacy and Protocol for DBA2 Test: Prevention of Audiogenic Seizures in DBA/2 Mice

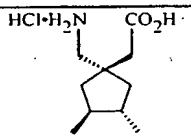
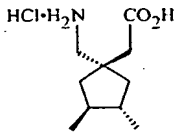
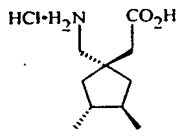
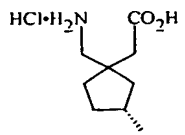
Methods

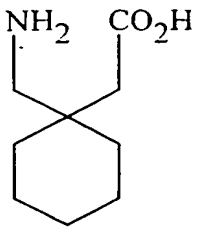
Results

The dose-dependent suppression of sound-induced tonic seizures in DBA/2 mice was tested, and the corresponding ED_{50} values are shown in Table 1.

The present results show that the compounds of the invention given orally cause dose-related anticonvulsant effects in a sound susceptible strain (DBA/2) of mice, confirming previous data showing anticonvulsant activity in other models of experimental epilepsy. The effective dosages of drugs in this model are lower than those in the maximal electroshock test, confirming that DBA/2 mice are a sensitive model for detecting anticonvulsant actions.

TABLE 1

			Carrageenan Induced Thermal Hyperalgesia in the Rat		DBA/2 Audiogenic Mouse
Compound	Structure	IC_{50} (μM) at $\alpha_2\delta$ binding site	% MPE[a] 1 hr postdose @ 30 mg/kg PO	% MPE[a] 2 hr postdose @ 30 mg/kg PO	% Protected 1 hr postdose 30 mg/kg PO
(±)-(trans)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride		0.034	23	72	100
(+)-(trans)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride		0.022	109	118	100
(-)-(trans)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride		1.0			
(cis/trans)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride		0.088	67	53	100



The compounds of the invention are also expected to be useful in the treatment of epilepsy.

The present invention also relates to therapeutic use of the compounds of the mimetic as agents for neurodegenerative disorders.

Such neurodegenerative disorders are, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis.

The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular incident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia such as in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like.

Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a

MATERIAL AND METHODS

Carrageenin-Induced Hyperalgesia

Nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesymeter (Randall-Sellitto Method: Randall L.O., Sellitto J.J., A method for measurement of analgesic activity on inflamed tissue. *Arch. Int. Pharmacodyn.*, 1957;4:409-419). Male Sprague-Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat and nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent any tissue damage to the paw. On the test day, two to three baseline measurements were taken before animals were administered 100 µL of 2% carrageenin by intraplantar injection into the right hind paw. Nociceptive thresholds were taken again 3 hours after carrageenin to establish that animals were exhibiting hyperalgesia. Animals were dosed with either gabapentin (3-300 mg/kg, s.c.), morphine (3 mg/kg, s.c.), or saline at 3.5 hours after carrageenin and nociceptive thresholds were examined at 4, 4.5, and 5 hours post-carrageenin.

Semicarbazide-Induced Tonic Seizures

Tonic seizures in mice are induced by subcutaneous administration of semicarbazide (750 mg/kg). The latency to the tonic extension of forepaws is noted. Any mice not convulsing within 2.0 hours after semicarbazide are considered protected and given a maximum latency score of 120 minutes.

Animals

Male Hooded Lister rats (200-250 g) are obtained from Interfauna (Huntingdon, UK) and male TO mice (20-25 g) are obtained from Bantin and Kingman (Hull, UK). Both rodent species are housed in groups of six. Ten Common Marmosets (Callithrix Jacchus) weighing between 280 and 360 g, bred at Manchester University Medical School (Manchester, UK) are housed in pairs. All animals are housed under a 12-hour light/dark cycle (lights on at 07.00 hour) and with food and water ad libitum.

Marmoset Human Threat Test

The total number of body postures exhibited by the animal towards the threat stimulus (a human standing approximately 0.5 m away from the marmoset cage and staring into the eyes of the marmoset) is recorded during the 2-minute test period. The body postures scored are slit stares, tail postures, scent marking of the cage/perches, piloerection, retreats, and arching of the back. Each animal is exposed to the threat stimulus twice on the test day before and after drug treatment. The difference between the two scores is analyzed using one-way analysis of variance followed by Dunnett's t-test. All drug treatments are carried out SC at least 2 hours after the first (control) threat. The pretreatment time for each compound is 40 minutes.

Rat Conflict Test

Rats are trained to press levers for food reward in operant chambers. The schedule consists of alternations of four 4-minute unpunished periods on variable interval of 30 seconds signaled by chamber lights on and three 3-minute punished periods on fixed ratio 5 (by footshock concomitant to food delivery) signaled by chamber lights off. The degree of footshock is adjusted for each rat to obtain approximately 80% to 90% suppression of responding in comparison with unpunished responding. Rats receive saline vehicle on training days.

The compounds of the instant invention are also expected to be useful in the treatment of pain and phobic disorders (*Am. J. Pain Manag.*, 1995;5:7-9).

The compounds of the instant invention are also expected to be useful in treating the symptoms of manic, acute or chronic, single upside, or recurring. They are also expected to be useful in treating and/or preventing bipolar disorder (United States Patent Number 5,510,381).

Models of Irritable Bowel Syndrome

TNBS-Induced Chronic Visceral Allodynia In Rats

Injections of trinitrobenzene sulfonic (TNBS) into the colon have been found to induce chronic colitis. In human, digestive disorders are often associated with visceral pain. In these pathologies, the visceral pain threshold is decreased indicating a visceral hypersensitivity. Consequently, this study was designed to

Group A: mean of the colonic threshold in the test compound-treated group

Statistical analysis

Statistical significance between each group was determined by using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p < 0.05$.

Compounds

TNBS is dissolved in EtOH 30% and injected under a volume of 0.5 mL/rat. TNBS is purchased from Fluka.

Oral administration of the test compound or its vehicle is performed 1 hour before the colonic distension cycle.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula 1 or 1A or a corresponding pharmaceutically acceptable salt of a compound of Formula 1 or 1A.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

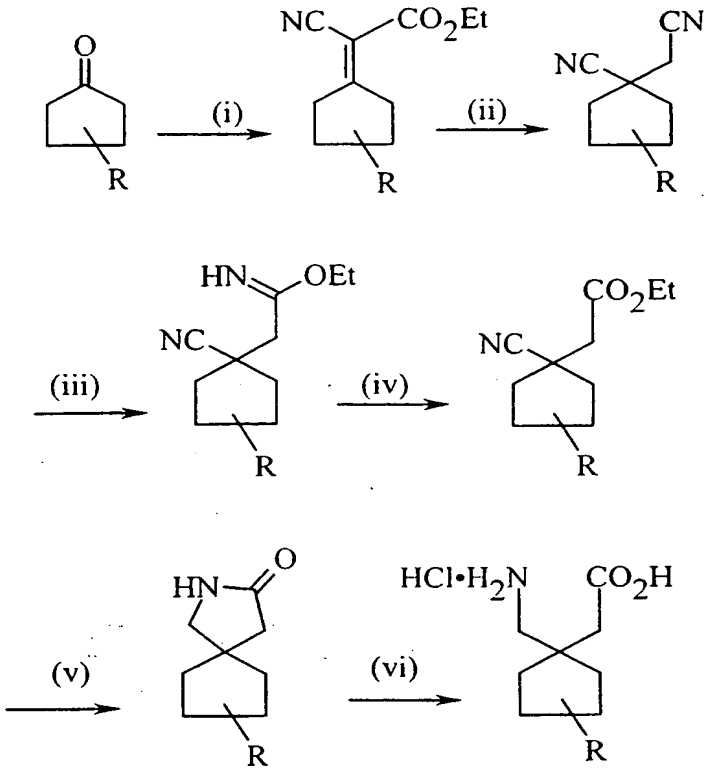
stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents.

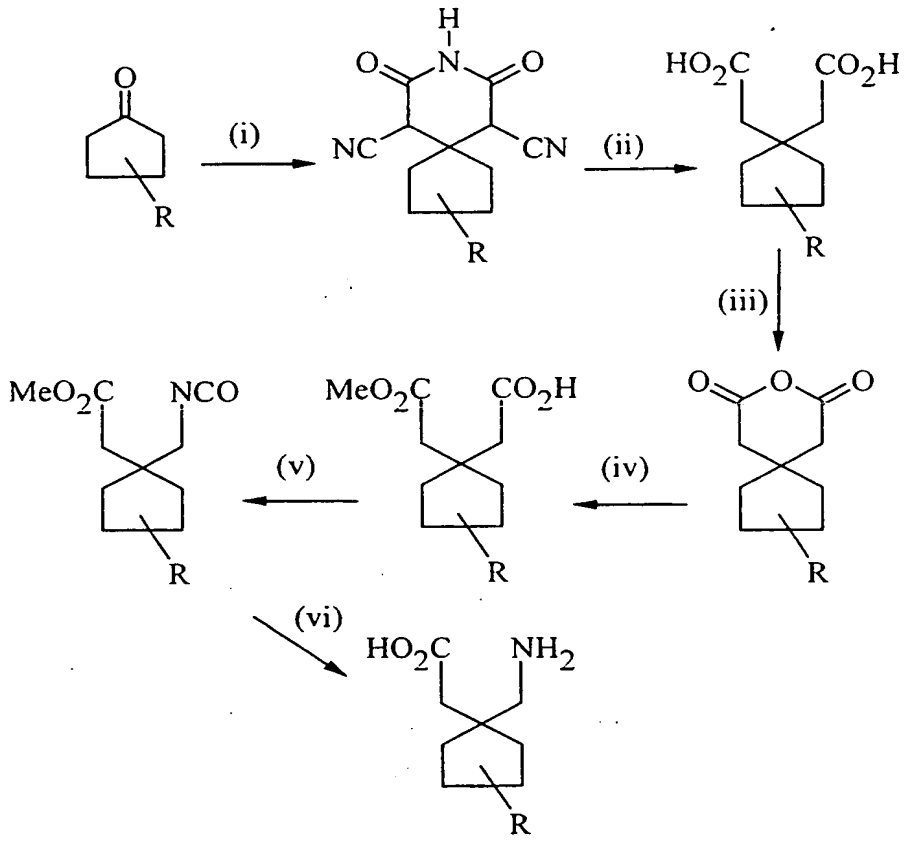
In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

General Scheme 1



(i) Ethyl cyanoacetate, piperidine (Cope et al., *J. Am. Chem. Soc.*,1941;63:3452); (ii) NaCN, EtOH/H_2O; (iii) EtOH, HCl; (iv) H_2O/H^+; (v) H_2, Rh/C, MeOH; (vi) HCl.

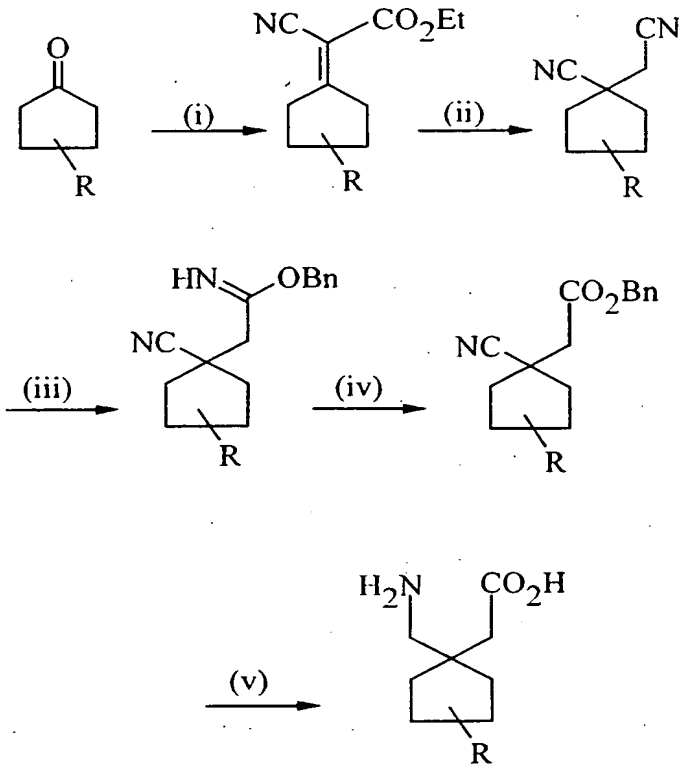
General Scheme 3



(i) Ethylcyanoacetate, ammonia then H_3O^+; (ii) H_2SO_4; (iii) Ac_2O; (iv) MeOH;

(v) Curtius Reaction; (vi) HCl, H_2O then anion exchange.

General Scheme 5



(i) Ethyl cyanoacetate, piperidine (Cope et al., *J. Am. Chem. Soc.*, 1941;63:3452); (ii) NaCN, $EtOH/H_2O$; (iii) BnOH, HCl; (iv) H_2O/H^+; (v) H_2, Rh/C, MeOH.

The following examples are illustrative of the instant invention; they are not intended to limit the scope.

In Examples 1 to 8, the first step involves the conversion of a cyclic ketone to an α,β-unsaturated ester **2** *via* use of a trialkylphosphonoacetate or an (alkoxycarbonylmethyl)triphenylphosphonium halide and a base, such as sodium hydride, potassium hydride, lithium- or sodium- or potassium-hexamethyldisilazide, butyllithium or potassium t-butoxide in a solvent such as tetrahydrofuran, dimethylformamide, diethylether or dimethylsulfoxide at a suitable temperature in the range from -78°C to 100°C.

The second step involves reaction of the α,β-unsaturated ester **2** with nitromethane and a suitable base such as tetrabutylammonium fluoride, tetramethylguanidine, 1,5-diazabicyclo[4,3,0]non-5-ene,

Synthesis of (trans)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester (2)

NaH (60% dispersion in oil, 737 mg, 18.42 mmol) was suspended in dry tetrahydrofuran (50 mL) and cooled to 0°C. Triethylphosphonoacetate (3.83 mL, 19.30 mmol) was added and the mixture stirred at 0°C for 15 minutes. The ketone **(1)** (1.965 g, 17.54 mmol) in THF (10 mL) was then added and the mixture allowed to warm to room temperature. After 2 hours, the mixture was partitioned between diethyl ether (200 mL) and water (150 mL). The organic phase was separated, washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane 1:9) to give 3.01 g (94%) of **(2)** as a colorless oil.

^1H NMR 400 MHz ($CDCl_3$): δ 1.01 (3H, d, J = 6 Hz), 1.03 (3H, d, J = 6 Hz), 1.26 (3H, t, J = 7 Hz), 1.49 (2H, m), 2.07 (1H, m), 2.24 (1H, m), 2.61 (1H, m), 4.13 (2H, q, J = 7 Hz), 5.72 (1H, s).

MS (CI+) m/e: 183 ([MH^+], 18%).

Synthesis of (trans)-(3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester (3)

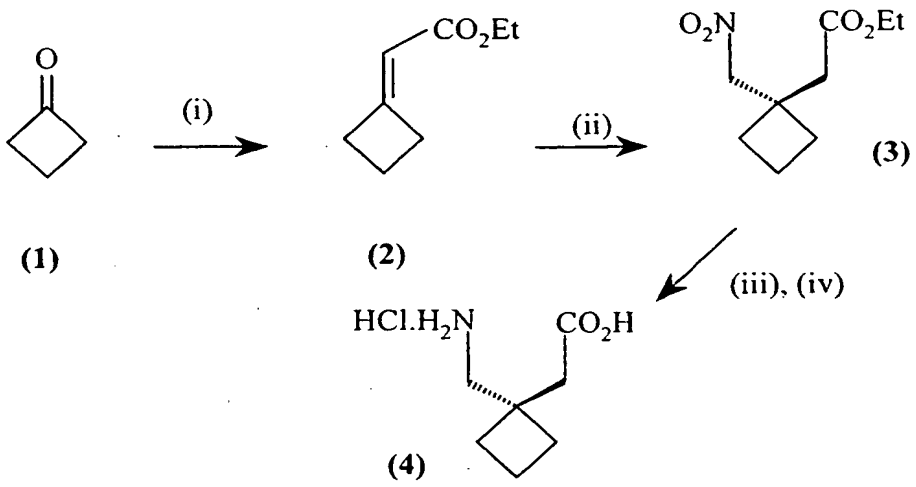
The unsaturated ester **(2)** (2.95 g, 16.2 mmol) was dissolved in tetrahydrofuran (10 mL) and stirred at 70°C with nitromethane (1.9 mL, 35.2 mmol) and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 22 mL, 22.0 mmol). After 6 hours, the mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with 2N HCl (30 mL) followed by brine (50 mL). The organic phase was collected, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane 1:9) to give 1.152 g (29%) of a clear oil.

^1H NMR 400 MHz ($CDCl_3$): δ 0.98 (6H, d, J = 6 Hz), 1.10-1.39 (5H, m), 1.47 (2H, m), 1.87 (1H, m), 2.03 (1H, m), 2.57 (2H, ABq, J = 16, 38 Hz), 4.14 (2H, q, J = 7 Hz), 4.61 (2H, ABq, J = 12, 60 Hz).

MS (ES+) m/e: 244 ([MH^+], 8%).

IR (film) ν cm^{-1}: 1186, 1376, 1549, 1732, 2956.

EXAMPLE 2



Reagents: (i) Triethylphosphonoacetate, NaH; (ii) $MeNO_2$, $Bu_4N^+F^-$; (iii) H_2, Ni; (iv) HCl

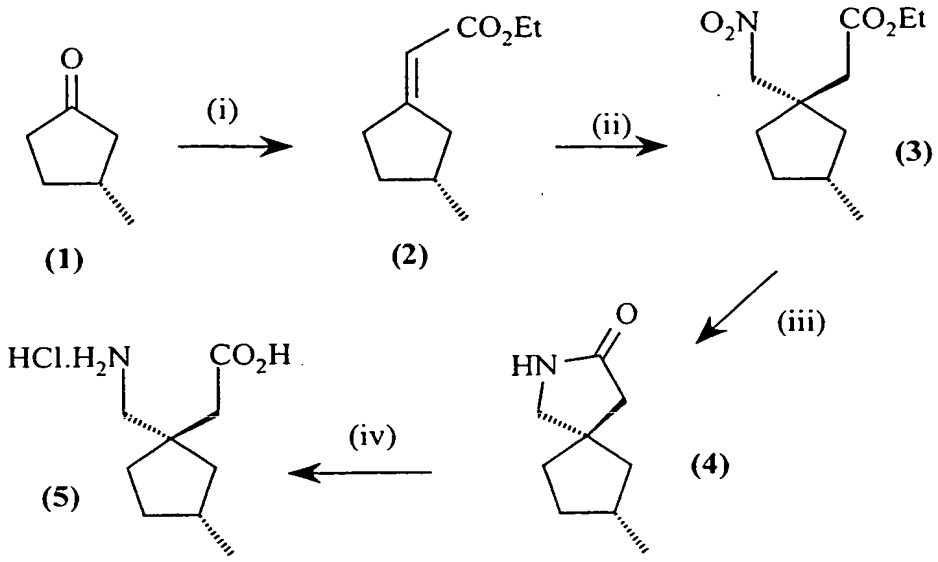
Synthesis of Cyclobutylidene-acetic acid ethyl ester (2)

NaH (60% dispersion in oil, 1.80 g, 44.94 mmol) was suspended in dry tetrahydrofuran (80 mL) and cooled to 0°C. Triethylphosphonoacetate (9.33 mL, 47.08 mmol) was added and the mixture stirred at 0°C for 15 minutes. Cyclobutanone **(1)** (3.0 g, 42.8 mmol) in THF (20 mL) was then added and the mixture allowed to warm to room temperature. After 2 hours, the mixture was partitioned between diethyl ether (200 mL) and water (150 mL). The organic phase was separated, washed with brine, dried ($MgSO_4$), and the solvent removed in vacuo at 600 mm Hg. The residue was purified by flash chromatography (silica, ethyl acetate:pentane 1:19) to give 5.81 g (96%) of **(2)** as a colorless oil.

^1H NMR, 400 MHz ($CDCl_3$): δ 1.27 (3H, t, J=6Hz), 2.09 (2H, m), 2.82 (2H, m), 3.15 (2H, m), 4.14 (2H, q, J = 6 Hz), 5.58 (1H, s).

MS (ES+) m/e: 141 ([MH^+], 100%). IR (film) ν cm^{-1}: 1088, 1189, 1336, 1673, 1716, 2926.

EXAMPLE 3



Reagents: (i) Triethylphosphonoacetate, NaH; (ii) $MeNO_2$, $Bu_4N^+F^-$; (iii) H_2, Ni; (iv) HCl

Synthesis of (R)-(3-Methyl-cyclopentylidene)-acetic acid ethyl ester (2)

NaH (60% dispersion in oil, 1.86 g, 46.5 mmol) was suspended in dry tetrahydrofuran (40 mL) and cooled to 0°C. Triethylphosphonoacetate (9.69 mL, 48.8 mmol) was added and the mixture stirred at 0°C for 15 minutes. The ketone **(1)** (5 ml, 46.5 mmol) in THF (10 mL) was then added and the mixture allowed to warm to room temperature. After 2 hours, the mixture was partitioned between diethyl ether (200 mL) and water (150 mL). The organic phase was separated, washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane 1:9) to give 5.45 g (70%) of **(2)** as a colorless oil.

^1H NMR 400 MHz ($CDCl_3$): δ 1.04 (3H, m), 1.27 (3H, t, J = 7 Hz), 1.80-2.74 (7H, m), 2.90-3.15 (1H, m), 4.13 (2H, q, J = 7 Hz), 5.76 (1H, s).

MS (CI+) m/e: 169 ([MH^+], 20%).

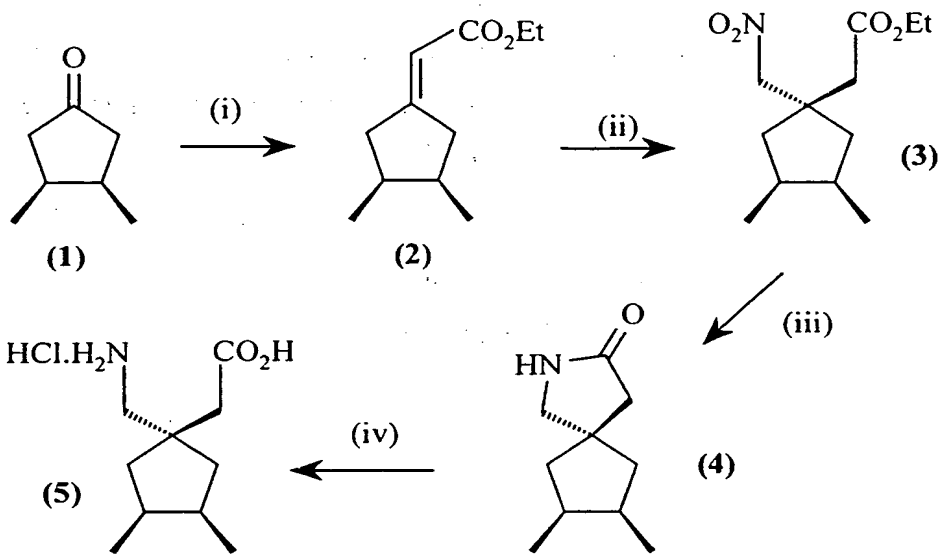
IR (film) ν cm^{-1}: 1205, 1371, 1653, 1716, 2955.

(3 × 30 mL). The aqueous phase was collected and the solvent removed in vacuo. The residue was triturated with ethyl acetate to give a white solid which was collected and dried. This was recrystallized from ethyl acetate/methanol to give 656 mg (65%) of **(5)** after collection and drying.

^{1}H NMR 400 MHz (d_6-DMSO): δ 0.96 (3H, m), 1.01-1.24 (2H, m), 1.42-2.10 (5H, m), 2.41 and 2.44 (2H total, 2 × s, cis/trans), 2.94 (2H, m), 7.96 (3H, br s), 12.35 (1H, br s).

MS (ES+) m/e: 172 ([MH-HCl]$^+$, 100%).

EXAMPLE 4



Reagents: (i) Triethylphosphonoacetate, NaH; (ii) $MeNO_2$, $Bu_4N^+F^-$; (iii) H_2, Ni; (iv) HCl

Synthesis of (cis)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester (2)

NaH (60% dispersion in oil, 519 mg, 12.96 mmol) was suspended in dry tetrahydrofuran (30 mL) and cooled to 0°C. Triethylphosphonoacetate (2.68 mL, 13.5 mmol) was added and the mixture stirred at 0°C for 15 minutes. The ketone **(1)** (1.21 g, 10.80 mmol) in THF (10 mL) was then added and the mixture allowed to warm to room temperature. After 2 hours, the mixture was partitioned

^{1}H NMR 400 MHz ($CDCl_3$): δ 0.89 (6H, d, J = 6 Hz), 1.38 (2H, m), 1.91 (2H, m), 2.10 (2H, m), 2.32 (2H,s), 3.18 (2H, s), 5.61 (1H, br s).

MS (ES+) m/e: 168 ([MH^+], 100%).

IR (film) ν cm^{-1}: 1304, 1450, 1699, 2871, 3186.

Synthesis of (1α,3β,4β)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride (5)

The lactam **(4)** (563 mg, 4.40 mmol) was heated to reflux in a mixture of 1,4-dioxan (5 mL) and 6N HCl (15 mL). After 4 hours, the mixture was cooled to room temperature, diluted with water (20 mL), and washed with dichloromethane (3 × 30 mL). The aqueous phase was collected and the solvent removed in vacuo. The residue was triturated with ethyl acetate to give a white solid which was collected and dried. This was recrystallized from ethyl acetate/methanol to give 440 mg (59%) of **(5)** after collection and drying.

^{1}H NMR 400 MHz (d_6-DMSO): δ 0.84 (6H, d, J = 6 Hz), 1.21 (2H, m), 1.81 (2H, m), 2.06 (2H, m), 2.47 (2H, s), 2.89 (2H, s), 7.94 (3H, br s), 12.30 (1H, br s).

MS (ES+) m/e: 186 ([MH-HCl]$^+$, 100%).

MS (ES+) m/e: 231 ([MH^+], 8%).

IR (film) ν cm^{-1}: 1190, 1335, 1675, 1715, 2980.

Synthesis of (cis/trans)-(3-Benzyl-1-nitromethyl-cyclobutyl)-acetic acid ethyl ester (3)

The unsaturated ester **(2)** (2.17 g, 9.42 mmol) was dissolved in tetrahydrofuran (15 mL) and stirred at 70°C with nitromethane (1.02 mL, 18.8 mmol) and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 14 mL, 14.0 mmol). After 24 hours, the mixture was cooled to room temperature, diluted with ethyl acetate (150 mL), and washed with 2N HCl (60 mL) followed by brine (100 mL). The organic phase was collected, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane 1:1) to give 1.55g (57%) of a clear oil.

^1H NMR 400 MHz ($CDCl_3$): δ 1.25 (3H, m), 1.86 (2H, m), 2.09-2.33 (2H, m), 2.53-2.78 (3H, m), 4.15 (2H, q, J = 6 Hz), 4.62 and 4.71 (2H total, 2 × s, cis/trans), 7.08-7.34 (5H, m).

MS (ES+) m/e: 292 ([MH^+], 100%).

IR (film) ν cm^{-1}: 1185, 1378, 1549, 1732, 2933.

Synthesis of (cis/trans)-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid hydrochloride (4)

The nitroester **(3)** (1.53 g, 5.25 mmol) was dissolved in methanol (50 mL) and shaken over Raney nickel catalyst under an atmosphere of hydrogen (45 psi) at 30°C. After 5 hours, the catalyst was removed by filtration through celite. The solvent was removed in vacuo to give 1.32 g of a pale yellow oil which was used without purification. The oil was dissolved in 1,4-dioxane (5 mL) and 6N HCl (15 mL) and heated to reflux. After 4 hours, the mixture was cooled to room temperature, diluted with water (20 mL) and washed with dichloromethane (3 × 30 mL). The aqueous phase was collected and the solvent removed in vacuo. The residue was triturated with ethyl acetate to give 0.88 g (62%) of a white solid after collection and drying.

Synthesis of (trans)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester (2)

To a suspension of sodium hydride (1.3 g, 32.5 mmol) in THF (60 mL) under nitrogen at 0°C was added triethylphosphonoacetate (6.5 mL, 32.7 mmol) over 5 minutes. After stirring for a further 10 minutes, a solution of **(1)** (approx. 2.68 g, approx. 30 mmol) in THF (2 × 10 mL) was added to the now clear solution and the ice bath removed. After 4 hours the reaction was quenched by pouring into water (100 mL) and the mixture extracted with ether (400 mL). The organic phase was washed with saturated brine (100 mL), dried and concentrated in vacuo. Column chromatography (10:1 heptane/ethyl acetate) gave the product as an oil, 4.53 g, approx. 100%; 91%.

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.01 (3H, d, J = 6 Hz), 1.03 (3H, d, J = 6 Hz), 1.26 (3H, t, J = 7 Hz), 1.49 (2H, m), 2.07 (1H, m), 2.24 (1H, m), 2.61 (1H, m), 4.13 (2H, q, J = 7 Hz), 5.72 (1H, s).

MS (CI+) m/e: 183 ([MH^+], 21%).

Synthesis of (trans)-(3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester (3)

To a solution of **(2)** (4.24 g, 23.3 mmol) in THF (15 mL) was added TBAF (32 mL of a 1 M solution in THF, 32 mmol) followed by nitromethane (3 mL) and the reaction heated at 60°C for 8 hours. After cooling, the reaction mixture was diluted with ethyl acetate (150 mL) and washed with 2N HCl (40 mL) then saturated brine (50 mL). Column chromatography (10:1 heptane/ethyl acetate) gave the product as an oil, 2.24 g, 40%.

^{1}H NMR 400 MHz ($CDCl_3$): δ 0.98 (6H, d, J = 6 Hz), 1.10-1.39 (5H, m), 1.47 (2H, m), 1.87 (1H, m), 2.03 (1H, m), 2.57 (2H, ABq, J = 16, 38 Hz), 4.14 (2H, q, J = 7 Hz), 4.61 (2H, ABq, J = 12, 60 Hz).

MS (ES+) m/e: 244 ([MH^+], 5%).

IR (film) ν cm^{-1}: 1186, 1376, 1549, 1732, 2956.

Ketone **(1)** is known in the literature and can be synthesized by the methods outlined therein: W. C. M. C. Kokke, F. A. Varkevisser, *J. Org. Chem.*, 1974;39:1535; Carnmalm, *Ark. Kemi*, 1960;15:215, 219; Carnmalm, *Chem. Ind.*, 1956:1093; Linder et al., *J. Am. Chem. Soc.*, 1977;99:727, 733; A. E. Greene, F. Charbonnier, *Tet. Lett.*, 1985;26:5525 and related references: R. Baker, D. C. Billington, N. Eranayake, *JCS Chem. Comm.*, 1981:1234; K. Furuta, K. Iwanaga, H. Yamamoto, *Tet. Lett.*, 1986;27:4507; G. Solladie, O. Lohse, *Tet. Asymm.*, 1993;4:1547; A. Rosenquist, I. Kvarnstrom, S. C. T. Svensson, B. Classon, B. Samuelsson, *Acta Chem. Scand.*, 1992;46:1127; E. J. Corey, W. Su, *Tet. Lett.*, 1988;29:3423; D. W. Knight, B. Ojhara. *Tet. Lett.*, 1981;22:5101.

Synthesis of (trans)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester (2)

To a suspension of sodium hydride (0.824 g, 20.6 mmol) in THF (40 mL) under nitrogen at 0°C was added triethylphosphonoacetate (4.1 mL, 20.7 mmol) over 5 minutes. After stirring for a further 10 minutes, a solution of **(1)** (approx. 2.10 g, approx. 15.8 mmol) in THF (2 × 10 mL) was added to the now clear solution and the ice bath removed. After 4 hours, the reaction was quenched by pouring into water (100 mL) and the mixture extracted with ether (4 × 100 mL). The organic phase was washed with saturated brine (50 mL), dried and concentrated in vacuo. Column chromatography (10:1 heptane/ethyl acetate) gave the product as an oil, 2.643 g, approx. 100%; 91%.

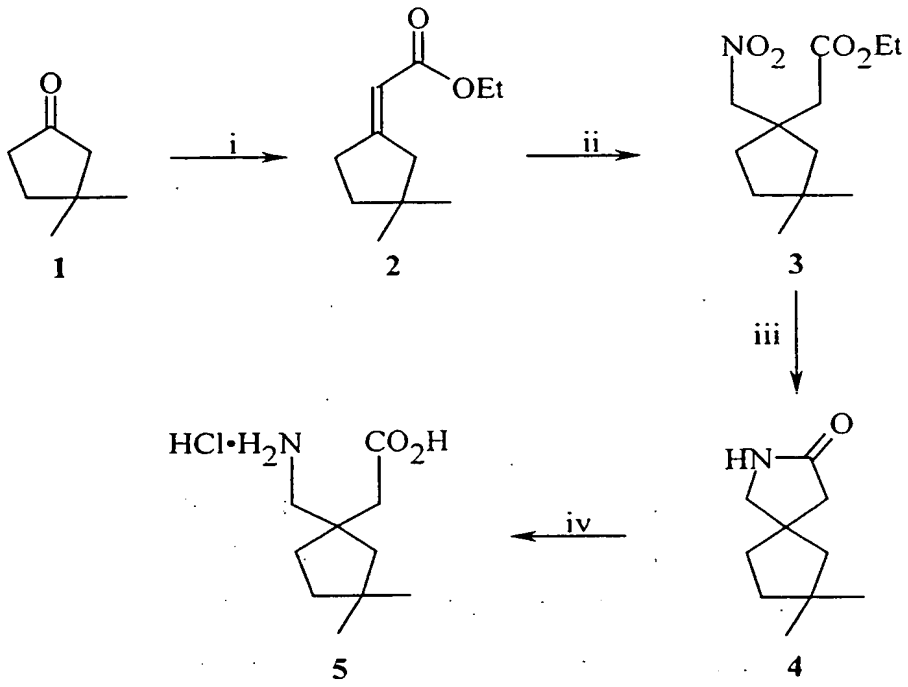
^{1}H NMR 400 MHz ($CDCl_3$): δ 1.01 (3H, d, J = 6 Hz), 1.03 (3H, d, J = 6 Hz), 1.26 (3H, t, J = 7 Hz), 1.49 (2H, m), 2.07 (1H, m), 2.24 (1H, m), 2.61 (1H, m), 4.13 (2H, q, J = 7 Hz), 5.72 (1H, s).

MS (CI+) m/e: 183 ([MH^+], 19%).

Synthesis of (trans)-(3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid ethyl ester (3)

To a solution of **(2)** (2.44 g, 13.4 mmol) in THF (12 mL) was added TBAF (18 mL of a 1 M solution in THF, 18 mmol) followed by nitromethane (2 mL) and the reaction heated at 60°C for 4 hours. After cooling, the reaction mixture was diluted with ethyl acetate (250 mL) and washed with 2N HCl (50 mL) then

EXAMPLE 8



Reagents and conditions: (i) $(EtO)_2POCH_2CO_2Et$, NaH, THF; (ii) CH_3NO_2, nBu_4NF, THF; (iii) RaNi, H_2, MeOH; (iv) 6N HCl.

Synthesis of the dimethylcyclopentanone 1

3,3-Dimethylcyclopentanone was prepared according to the procedure of Hiegel and Burk, *J. Org. Chem.*, 1973;38:3637.

Synthesis of (3,3-Dimethyl-cyclopentylidene)-acetic acid ethyl ester (2)

To a stirred solution of triethylphosphonoacetate (1.84 g, 7.52 mmol) in THF (20 mL) at 0 C was added sodium hydride (300 mg of a 60% dispersion in oil). After 30 minutes, the ketone **1** (766 mg, 6.84 mmol) in THF (5 mL) was added. After 24 hours, the solution was diluted with a saturated solution of ammonium chloride and the two phases separated. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and dried ($MgSO_4$). The combined organic phases were concentrated and flash chromatographed (25:1 hexane/ethyl acetate) to give the ester **2** as an oil, (697 mg, 56%).

Synthesis of (±)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid hydrochloride (5)

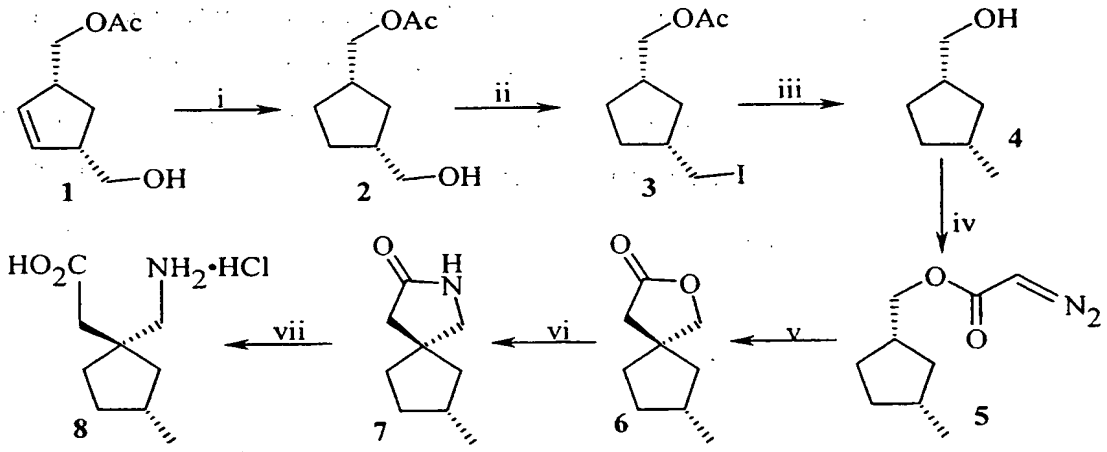
The lactam (240 mg, 1.44 mmol) in 6N HCl were heated to reflux for 24 hours. The residue was concentrated under reduced pressure and triturated with ether to give the amino acid **5** as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ 2.98 (2H, s), 2.4 (2H, s), 1.5 (2H, m), 1.4-1.2 (4H, m), 0.84 (3H, s), 0.84 (3H, s).

MS (m/z): 186 (MH^+, 100%), 168 ($M-NH_3$, 20%).

EXAMPLE 9

Synthesis of (cis)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride



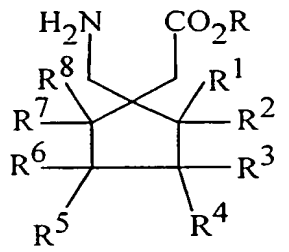
Reagents and conditions: (i) H_2, Pd/C, MeOH; (ii) I_2, Ph_3P, imidazole, CH_3CN; (iii) LAH, THF; (iv) TsNHN = CHCOCl, $PhNMe_2$, Et_3N; (v) $Rh_2(cap)_4$, CH_2Cl_2, reflux; (vi) a) BBr_3, EtOH; b) NH_3; (vii) 6N HCl, reflux.

The monoester **1** was prepared according to the procedure described in *Tetrahedron: Asymmetry* 3, 1992:431.

In the first step, the ester **1** is hydrogenated using catalysts such as Raney nickel, palladium on charcoal or rhodium catalyst or other nickel or palladium containing catalyst in a solvent such as methanol, ethanol, isopropanol, ethyl

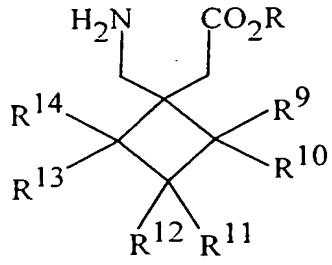
CLAIMS

1. A compound of formula



1

or



1A

or a pharmaceutically acceptable salt thereof wherein:

R is hydrogen or a lower alkyl;

R^1 to R^{14} are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbons, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, $-CO_2H$, $-CO_2R^{15}$, $-CH_2CO_2H$, $-CH_2CO_2R^{15}$, $-OR^{15}$ wherein R^{15} is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R^1 to R^8 are not simultaneously hydrogen.

2. A compound according to Claim 1 wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl straight or branched, phenyl, or benzyl.

3. A compound according to Claim 1 wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, or benzyl.

4. A compound according to Claim 1 and selected from:

(±)-(trans)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

cis-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-diethyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-diisopropyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-di-tert-butyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-diphenyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-dibenzyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-2,2,4,4-tetramethyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-2,2,3,3,4,4-hexamethyl-cyclobutyl)-acetic acid;

(R)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;

(S)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1R-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1R-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4β)- (1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-2,2,5,5-tetramethyl-cyclopentyl)-acetic acid;

(1α,2β,5β)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2R, 5R)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2S. 5S)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(1α,2α,5α)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

11. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

12. A method for treating panic comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

13. A method for treating pain comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

14. A method for treating neuropathological disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

15. A method for treating inflammation comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

16. A method for treating gastrointestinal disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

17. A method for treating irritable bowel syndromes comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

18. A compound selected from:

(trans)-(3,4-Dimethyl-cyclopentylidene)-acetic acid ethyl ester;
(trans)-(3,4-Dimethyl-1-nitromethyl-cyclopentyl)-acetic acid;
(±)-(trans)-7,8-Dimethyl-spiro[4.4]nonane-2-one;
(1-Nitromethyl-cyclobutyl)-acetic acid ethyl ester;

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/US 98/19876

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/28 C07C229/34 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 024 175 A (GERHARD SATZINGER ET AL.) 17 May 1977 cited in the application see claims; examples	1-18
Y	WO 97 33858 A (WARNER LAMBERT) 18 September 1997 see claims; examples	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 1999	08/03/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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